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An evaluation of vitamin D status in individuals with systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a multi-system inflammatory disease where genetic susceptibility coupled with largely undefined environmental factors is reported to underlie the aetiology of the disease. One such factor is low vitamin D status. The primary source of vitamin D is endogenous synthesis following exposure of the skin to UVB light. Photosensitivity, sunlight avoidance and the use of sun protection factor in combination with medications prescribed to treat the symptoms of the disease, puts SLE patients at increased risk of vitamin D deficiency. Decreased conversion of 25-hydroxyvitamin D to the metabolically active form, 1,25-dihydroxyvitamin D_3, is possible, due to renal impairment common in SLE putting additional stress on vitamin D metabolism. The majority of studies have identified low 25-hydroxyvitamin D in SLE patients, albeit using varying cut-offs (<25 to <80 nmol/l). Of these studies, fifteen have investigated a link between status and disease activity with conflicting results. Variation with disease activity index measures used alongside methodological limitations within the study design may partially explain these findings. This review discusses the importance of optimal vitamin D status in SLE, critically evaluates research carried out to date that has investigated vitamin D in SLE, and highlights the need for a well-designed observational study that controls for diet, medication use, dietary supplements, UV exposure and seasonality, that uses sensitive methods for measuring vitamin D status and disease activity in SLE to conclusively establish the role of vitamin D in SLE.

Systemic lupus erythematosus: Vitamin D status: 25-hydroxyvitamin D: Disease activity

Systemic lupus erythematosus (SLE) is a complex relapsing–remitting inflammatory autoimmune disease affecting various organ systems within the body resulting in numerous clinical and serological consequences[1]. The disease course is unpredictable with relapse/remitting phases of disease common. Symptoms include photosensitivity, facial rash, mouth ulcers, arthritis and fatigue and there is a nine-fold higher incidence in females, those of child-bearing age and of African–American or Asian descent[2]. Based on a study in Northern Ireland, in 1993, the prevalence of SLE was estimated to be 25·4 per 10 000 equating to 415 individuals in Northern Ireland diagnosed with the condition at that time[3].

The presentation and progression of SLE have been linked with a combination of environmental, genetic and hormonal factors[4,5]. One such environmental factor is vitamin D. The identification of vitamin D receptors on cells of the immune system and the discovery that dendritic cells can produce the metabolically active form of vitamin D, 1,25-dihydroxyvitamin D, have led to the suggestion that vitamin D is an immune modulator[6] and given that vitamin D deficiency-related symptoms such as fatigue are frequently observed in those with SLE[7]. Furthermore, it is postulated that SLE patients may be at increased risk of low vitamin D status as a result of photosensitivity and resultant sun avoidance together with the

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ECLAM, European consensus lupus activity measure; SLAM, systemic lupus activity measure; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.

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chronic use of medications prescribed in the management of SLE which interfere with vitamin D metabolism[8,9]. However, research has not established whether low vitamin D is a contributing factor to the development of SLE or is a consequence of the disease.

Vitamin D was first associated with bone health; however, recent evidence has identified vitamin D receptors in various bodily tissues including that of the immune system[10], with a resultant linkage suggested between vitamin D and autoimmune diseases including SLE[11–13]. Vitamin D exerts its effects on the immune system via 1,25-dihydroxyvitamin D_3[14] and vitamin D inadequacy in animal models has been shown to contribute to the development of autoimmunity with vitamin D treatment resulting in an improvement of symptoms[11]. Vitamin D has been shown to act on the immune system through the regulation and differentiation of lymphocytes, macrophages and natural killer cells as well as preventing over expression of anti-inflammatory cytokines[11,15]. Translation of these effects into clinical practice for individuals diagnosed with SLE has received attention albeit only one study has evaluated SLE patients following clinical advice to take dietary vitamin D supplements[16]. The results showed an improvement in levels of fatigue, albeit, they did not identify an improvement in overall disease activity[16].

Over the past 15 years, and in particular in the last 5 years, research has reported that SLE patients have significantly lower vitamin D status than their healthy counterparts[12,17–21]. Some have reported an association between vitamin D status and disease activity with lower vitamin D status contributing to greater disease activity[17–20,22–25]. An association between vitamin D and fatigue has also been reported[16,26]; however, not all studies have observed a relationship between vitamin D and indices of disease activity in SLE[27–30]. Therefore, currently there is no clear consensus regarding the role of vitamin D in the progression and/or management of SLE. The lack of agreement may be explained by a number of methodological limitations in studies carried out to date. In critically evaluating studies that have investigated vitamin D status and disease activity in SLE as well as those that have compared 25-hydroxyvitamin D (25(OH)D) concentrations between SLE patients and control cohorts, this review will discuss potential methodological strengths and limitations in studies conducted to date.

Vitamin D status in systemic lupus erythematosus compared to control populations

As a result of medications commonly prescribed in SLE, sunlight avoidance and the use of sun protection factor, it is postulated that individuals with SLE may have lower vitamin D status compared to their healthy, disease-free counterparts. The observation that the incidence of some autoimmune diseases increases further from the equator has prompted interest in factors such as low UV radiation exposure, possibly acting via vitamin D status that may explain this gradient[31]. A study in the UK investigating SLE incidence rates demonstrated higher incidence at more northerly latitudes, however, no clear associations with latitude were found[32].

The majority of studies conducted to date have reported significantly lower vitamin D status in individuals with SLE compared to controls[12,17–21]; however, some studies have indicated no significant difference in serum 25(OH)D concentrations between SLE patients and controls[33–35] (Table 1). Taking into consideration the line of latitude that the study was conducted does not appear to explain the variations of vitamin D status of those with SLE (Table 1) and suggests that other factors are impacting on status in this group. Further epidemiological studies are required specifically with SLE to establish if a latitude gradient exists.

It is noteworthy that those studies which did not identify any significant difference in serum 25(OH)D concentrations between the SLE patients and the control group did not use power calculations to determine their sample size, which may have resulted in the study being underpowered to detect any difference. Furthermore, some of the studies[33–35] were conducted in countries with a latitude >40°N where vitamin D status would be expected to be low among the general population as well as those individuals with SLE, given that sunlight would be too weak to stimulate vitamin D synthesis for 6 months of the year in these countries[36]. One study conducted between January and March in Ontario, Canada, during which time vitamin D stores would have reached their nadir, used fibromyalgia patients as their control cohort[33]. Sub-optimal levels of vitamin D and vitamin D deficiency have been associated with fatigue[37], one of the most common symptoms for fibromyalgia patients. This patient group is therefore not ideal to act as a control population when examining vitamin D status in SLE. To improve the validity of a study, it is necessary to select an appropriate control group when making comparisons. Studies that have shown vitamin D status is significantly lower in SLE have all selected free living and apparently healthy control groups[12,17–21] making their findings more robust.

Prevalence of vitamin D inadequacy in systemic lupus erythematosus: impact of varying cut-offs

Literature examining vitamin D status in SLE patients includes a variety of cut-offs for vitamin D sufficiency and deficiency (Table 1). Two studies involving Asian cohorts utilised >75 nmol/l to represent vitamin D sufficiency and <50 nmol/l as vitamin D deficiency[19,20]. Damanhouri[20] based cut-offs for sufficient vitamin D status (75 nmol/l) in Saudi SLE patients based on a review by Holick[38]. Research in Saudi populations previously used cut-offs in the range of 25–50 nmol/l to denote sufficient vitamin D status; however, more recently a threshold of 75 nmol/l is considered to represent vitamin D sufficiency[39]. The levels of adequate vitamin D status in these two studies[19,20] varies, with 83·7% of the Korean cohort and 1·2% of the Saudi SLE patients having adequate serum 25(OH)D concentrations, respectively. A likely explanation for the difference observed here could be the veiling of females in Saudi Arabia, highlighting the high prevalence of vitamin D inadequacy in groups who cover their skin due to religious beliefs. It is worth noting that the Saudi SLE group had significantly lower vitamin D status

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Table 1. Summary of studies conducted to date, which have investigated vitamin D status in systemic lupus erythematosus (SLE). 25-hydroxy vitamin D (25(OH)D) concentrations are reported as means unless otherwise stated

Reference	Country (latitude)	Season	SLE cohort	*n* (SLE *v.* Control)	Cut-off for 25(OH)D inadequacy (nmol/l)	Inadequate 25(OH)D (% of SLE patients)	Mean 25(OH)D (nmol/l) (SLE *v.* Control)	Result (25(OH)D)
(33)	Ontario (48°N)	January–March	All female	25 *v.* 25†	<50	58	47 *v.* 52	NS
(35)	Austria (46–49°N)	NR	All female	30 *v.* 39	NR	NR	69 *v.* 53	NS
(34)	Germany (48–54°N)	NR	All female	20 *v.* 35 *v.* 20‡	NR	NR	68 *v.* 49 *v.* 101	NS
(30)	Copenhagen (55°N)	NR	1M, 20F	21 *v.* 72	NR	NR	33 *v.* 67 §	↓ in SLE*
(21)	Shanghai (31°N)	NR	11M, 101F	112 *v.* 28	NR	NR	29 *v.* 148	↓ in SLE*
(19)	Korea (37–40°N)	March–May	All female	104 *v.* 49	<75	16	106 *v.* 132	↓ in SLE*
(18)	Philadelphia (39°N)	NR	Paediatric 7M, 31F	38 *v.* 207	≤ 75	76	45 *v.* 56	↓ in SLE*
(17)	Sao Paulo (23°S)	Summer–Autumn	All female	12 *v.* 24 *v.* 26‖	<50	83	43 *v.* 111 *v.* 94	↓ in SLE*
(20)	Saudi Arabia (25°N)	January–June	17M, 148F	165 *v.* 214	<75	99	24 s. 65	↓ in SLE*
(12)	Carolina (33–35°N)	All year	NR	123 *v.* 240	<75	67	54 *v.* 68	↓ in SLE**
(44)	Amsterdam (52°N)	All year	99F	107¶	<25	8	NR	NA
(27)	Spain (40°N)	All year	7M, 48F	55¶	<75	86	57	NA
(16)	Spain (40°N)	October–November	8M, 72F	80¶	<75	71	62	NA
(24)	Hungary (47°N)	July	17M, 160F	177¶	<75	82	67	NA
(28)	Toronto (43°N)	All year	All female	124¶	<80	67	69	NA
(69)	New York (40°N)	All year	14M, 109F	123	<75	86	45	NA
(25)	Chicago (41°N)	NR	All female	181¶	<75	62	68	NA
(26)	Texas (31°N)	NR	All female	37¶	<80	65	77	NA
(29)	Spain (40°N)	All year	9M, 83F	92¶	<75	75	55	NA
(45)	Hungary (47°N)	NR	All male	23 *v.* 40	≤ 45	65	40	NA
(22)	Europe and Israel (31–48°N)	NR	31M, 347F	278 and 100¶	NR	NR	60 and 69	NA
(23)	USA (27–44°N)	NR	14M, 184F	140 *v.* 42 *v.* 6 *v.* 10††	NR	NR	35 *v.* 51 *v.* 55 *v.* 72§	NA
(57)	NR	NR	NR	138¶	NR	NR	30 *v.* 54	NA

NR, not reported; NS, non-significant; NA, not assessed; M, male; F, female.
†Control group comprised fibromyalgia patients.
‡Cohort comprised SLE patients not on steroids *v.* SLE patients on steroids *v.* controls.
§Median.
‖Cohort comprised SLE patients with high *v.* minimal disease activity *v.* controls.
¶SLE patients only.
††SLE patients subdivided based on ethnicity: African Americans *v.* Hispanics *v.* Asians *v.* Caucasians *$P<0·05$, **$P<0·05$ in Caucasians only.

when compared with a control group of Saudi women suggesting that other factors could be contributing to the decreased vitamin D status observed in SLE.

The majority of studies carried out in North and South America define serum 25(OH)D concentrations >75 nmol/l as sufficient vitamin D status and <50 nmol/l as vitamin D deficiency[17,18,25,28,33]. Two studies report serum 25(OH)D concentrations in the range of 75–80 nmol/l as deficient vitamin D status[12,26]. A number of these studies report using these cut-offs based on reviews in the area of vitamin D[38,40–43]. Cut-offs used by European research groups vary slightly. Ruiz-Irastorza *et al.*, in agreement with the American and Asian studies, report <75 and <50 nmol/l to represent insufficient and deficient vitamin D status, respectively[16,29]. However, much lower cut-offs for vitamin D deficiency have been reported by Bultink *et al.* (<25 nmol/l)[44] and Bhattoa *et al.* (<12·5 nmol/l)[45]. The latter two studies were published a number of years ago and evidence has been accumulating more recently of the benefits of higher serum 25(OH)D concentrations for multiple health outcomes[46]; therefore, the threshold for adequate vitamin D status has increased in more recent times.

Vitamin D recommendations have been largely based on the prevention of bone disease and for this reason serum 25(OH)D concentration ≥ 50 nmol/l have been considered as adequate vitamin D status. However, based on more recent research into the benefits of vitamin D beyond bone health, concentrations as great as 100 nmol/l have been proposed for many non-skeletal functions including immune function[41]. In 2010, an expert panel in the area of vitamin D made recommendations in relation to adequate serum 25(OH)D concentrations for clinical practice in musculoskeletal health, CVD and autoimmunity[46]. The majority of experts from the panel recommended serum 25(OH)D concentrations ranging from 75 to 100 nmol/l for multiple health outcomes, with the lower threshold set at 75 nmol/l to ensure that individuals have a true concentration >50 nmol/l[47,48]. Based on the conclusions of the expert panel there may be a move towards higher thresholds for vitamin D sufficiency in the literature. Albeit, the Institute of Medicine report does not

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support the suggestion that vitamin D has benefits beyond bone health. Recently this has been challenged where results from randomised controlled trials, observational studies, ecological studies and reviews suggest vitamin D to have many additional benefits addition to bone health[49]. This further supports the evidence put forth by the expert panel in vitamin D proposing 75 nmol/l as a target for adequate vitamin D status for immune function. If the higher threshold of 75 nmol/l were to be considered in all of the studies evaluated in this review, a larger proportion of SLE patients would be presenting with vitamin D inadequacy. The lack of consensus as to what defines insufficient vitamin D status by health agencies and organisations throughout the world may result in the misdiagnosis of individuals with vitamin D inadequacy. For individuals with SLE, this may have a direct impact on the treatment of their disease possibly exacerbating their symptoms.

Seasonal variation and disease activity in systemic lupus erythematosus

Photosensitivity is one of the most common clinical features in SLE and exposure to sunlight during the summer months is thought to exacerbate disease activity. Some studies have shown an accumulation of photosensitivity[50,51] or a greater incidence of rash[52] during the summer months. However, lack of statistical analysis weakens these findings and the results should be interpreted with this in mind.

Vitamin D is subject to seasonal variation, with higher concentrations at the end of summer which reaches a nadir at the end of winter. With this in mind it is postulated that disease activity could be increased during the winter/spring with some peaks of disease activity during the summer due to photosensitivity. A number of studies have investigated whether season contributes to flares of disease activity for individuals with SLE. One reported a significant increase in the European Consensus Lupus Activity Measure (ECLAM) during the spring with no worsening of disease activity during the summer[51]. Another identified a significant increase in disease activity scored by a clinical disease activity score during the winter compared to all other seasons[52]. Furthermore, another study reported increased prevalence in flares of disease activity and lupus nephritis in SLE patients from Hong Kong, during December and January, corresponding to winter[53]. Similarly, another study identified an increased prevalence of class V lupus nephritis during winter and spring[54]. The results from these studies provide some evidence to suggest more profound disease activity for SLE patients during the winter/spring, at which time vitamin D stores are depleting, suggesting a possible relationship exists between lower serum 25(OH)D, season and disease activity. However, there is insufficient evidence to make firm conclusions and the increased disease activity identified may be attributed to another factor not assessed in these studies such as a greater incidence of viral infections commonly seen throughout the winter months which has also been associated with lowered immunity due to vitamin D inadequacy[55]. Therefore, the evidence in this area is inconclusive and further research is warranted taking into account temperature, UV strength and humidity as possible factors contributing to photosensitivity and facial rash in SLE during spring and summer, as well as monitoring subject's hospitalisation levels, viral infections and general health.

The relationship between vitamin D status and disease activity in systemic lupus erythematosus

Vitamin D deficiency has been associated with a number of symptoms which may also be part of the aetiology of SLE; therefore, the relationship between vitamin D status and disease activity has been examined albeit with conflicting results. Damage and disease activity in SLE are assessed using a variety of validated scoring methods. The Systemic Lupus International Collaborating Clinician/American College for Rheumatology is a method for assessing damage in SLE patients and the systemic lupus erythematosus disease activity index (SLEDAI), systemic lupus activity measure (SLAM), the ECLAM and the British Isles Lupus Assessment Group are used for scoring disease activity. The majority of studies carried out to date have used SLEDAI in their assessment of disease activity (Table 2), two have used ECLAM whereas no study has used SLAM or British Isles Lupus Assessment Group. Although these assessment tools correlate well with each other, it has been shown that SLEDAI is least sensitive to change[56] and therefore, it may not be the best tool to examine the effect of vitamin D status on disease activity as vitamin D status can rapidly fluctuate depending on sun exposure, increased dietary intake and supplement use. Although comparison between studies is possible due to the common use of SLEDAI, use of additional assessment tools that are sensitive to changes in activity (e.g. SLAM) in future studies may strengthen findings.

An inverse association between serum 25(OH)D concentrations and disease activity, assessed by SLEDAI, has been reported[12,17–19,22–25]. The largest study undertaken to date, which combined several SLE cohorts scoring disease activity using the SLEDAI and ECLAM revealed a significant negative correlation between disease activity and serum 25(OH)D concentrations[22]. Furthermore, patients with active disease, represented as SLEDAI>3 or ECLAM >1, had significantly lower vitamin D status than patients with inactive disease. Those with inactive disease activity had mean serum 25(OH)D concentrations of 61 nmol/l, suggesting serum 25(OH)D concentrations >60 nmol/l may be protective against flares of disease activity[22].

A study of SLE patients from mixed ethnic backgrounds showed a significant correlation between vitamin D status and disease activity after controlling for ethnicity and prednisone dose[23]. Another study of children and adolescent SLE patients reported significantly greater SLEDAI scores among those with moderate vitamin D deficiency (25(OH)D<50 nmol/l) after adjusting for both ethnicity and BMI ($P = 0{\cdot}01$)[18]. An additional study of female SLE patients from the Chicago Lupus Database reported a

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Table 2. Associations between serum 25-hydroxyvitamin D (25(OH)D) concentrations and indices of disease activity in systemic lupus erythematosus (SLE) patients

Reference	Sample size	Disease activity marker	Result
(22)	378	SLEDAI and ECLAM*	Inverse correlation between 25(OH)D and disease activity ($r = -0{\cdot}12$, $P = 0{\cdot}018$)
(23)	198	SLEDAI	The degree of vitamin D deficiency correlated inversely with SLEDAI ($r = -0{\cdot}234$, $P = 0{\cdot}002$) controlling for ethnicity and prednisone dose
(19)	104	SLEDAI, C3 and Hb	25(OH)D correlated with C3 ($\beta = 0{\cdot}365$, $P = 0{\cdot}002$) and Hb ($\beta = 0{\cdot}256$, $P = 0{\cdot}018$) controlling for BMI
(16)	80	SLEDAI and VAS	Inverse association between 25(OH)D and VAS ($P = 0{\cdot}001$) independent of age, SLEDAI and HCQ
(24)	177	SLEDAI	Higher 25(OH)D was associated with lower SLEDAI ($P = 0{\cdot}038$)
(25)	181	SLEDAI and SDI	25(OH)D was associated with SLEDAI ($\beta = -0{\cdot}715$, $P = 0{\cdot}018$) controlling for age, seasonal variation and ethnicity, NS when further controlling for BMI
(17)	36	SLEDAI	25(OH)D was associated with SLEDAI ($r = -0{\cdot}58$)
(18)	38	SLEDAI	25(OH)D <25 nmol/l was associated with greater SLEDAI ($\beta = 3{\cdot}4$, $P = 0{\cdot}02$) adjusting for ethnicity and BMI
(26)	37	VAS	25(OH)D<47·5 nmol/l was associated with higher VAS ($P = 0{\cdot}003$)
(27)	55	SLEDAI	NS
(28)	124	SLEDAI-2K	NS
(29)	92	SLEDAI and VAS	NS
(21)	112	SLEDAI	NS
(57)	138	ECLAM	NS
(30)	21	Disease activity indices†	NS

SLEDAI, systemic lupus erythematosus disease activity index; NS, non-significant; VAS, visual analogue scale for the assessment of fatigue; ECLAM, European consensus lupus activity measure; C3, complement 3; HCQ, hydroxychloroquine; SDI, systemic damage index; ESR, erythrocyte sedimentation rate.
*SLEDAI and ECLAM score combined and converted to standardised Z score.
†Indices of disease activity include anti-DNA titres, ESR, Hb, thrombocyte and leucocyte concentrations.

significant inverse relationship between serum 25(OH)D and SLEDAI after adjusting for age, seasonal variation and race ($P = 0{\cdot}018$)[25]. However, after further adjustment for BMI, the relationship was no longer significant. This clearly demonstrates the need to control for all factors that will impact on vitamin D status in the analysis and may potentially explain why others have not found similar results[17,18,25,26].

A Brazilian cohort of SLE patients sub-divided based on disease activity found serum 25(OH)D to be significantly inversely related to SLEDAI ($P = 0{\cdot}001$)[17]. The inclusion criteria stipulated SLE patients with minimal disease activity (SLEDAI ≤ 3) or high disease activity (SLEDAI ≥ 12) and those with high disease activity had significantly lower serum 25(OH)D compared to the patients with minimal disease activity (serum 25(OH)D 43 nmol/l *v.* 111 nmol/l, respectively ($P<0{\cdot}001$))[17], suggesting serum 25(OH)D concentrations <50 nmol/l may have a more profound impact on disease activity compared to serum 25(OH)D concentrations >100 nmol/l. An additional study grouping SLE patients based on deficient, insufficient and sufficient vitamin D status reported increased disease activity in the deficient (<37·4 nmol/l) patient group[24], again supporting the theory that much greater concentrations of serum 25(OH)D are necessary to protect against flares. Strength of these studies is the sample size, with the majority of the studies recruiting large numbers of SLE patients suggesting that the cohorts were sufficiently powered to see a significant relationship.

However, several research groups have not shown a relationship between disease activity and vitamin D status in SLE patients[16,19,21,26–30,57]. Two studies scored disease activity in the SLE patients using clinical charts and not via patient consultation[21,30], with an additional study not including details on the methods for obtaining the clinical and serological information to score the ECLAM[57]. The preferred method for determining disease activity in SLE is via interview and therefore, the true extent of the patients' disease activity may have been over- or underestimated in these studies, masking any possible relationship. Another study examined inflammatory markers associated with disease activity in SLE and found no difference in serum 25(OH)D concentrations when those with active disease were compared with those presenting with less inflammatory activity[30]. Others did not report a significant association between serum 25(OH)D and SLEDAI[16,19,21,26–29] or ECLAM[57]. It is worth noting that although one of these studies did not identify an association with serum 25(OH)D and SLEDAI, they did report a significant association between 25(OH)D and fatigue[16]. Similarly a study of disease status in Texan SLE patients reported those with serum 25(OH)D concentrations <47·5 nmol/l had significantly higher fatigue scores ($P = 0{\cdot}003$)[26]. Fatigue is a debilitating symptom common in SLE, which is evaluated in the disease activity assessment tool SLAM, but not in SLEDAI. Using SLAM alongside other measures of disease activity would provide additional information of how vitamin D impacts on disease activity incorporating fatigue. Kim *et al.* found 25(OH)D to correlate with C3, an index of disease activity in SLE[19], which is also incorporated within the laboratory measures used to score SLAM. Therefore, some of the studies where an association was not identified between vitamin D and disease activity may be partly explained in that the disease

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assessment tool did not allow for this factor. The use of a combination of assessment tools would ensure that all factors are taken into consideration and allow for better comparisons to be made within the literature.

The method for measuring serum 25(OH)D is key when assessing vitamin D status, with various methods now available, such as enzyme immunoassay, RIA, chemiluminescent immunoassay, HPLC and liquid chromatography–tandem MS. Inconsistencies have been shown in serum 25(OH)D concentrations when different methods are used for the assessment of vitamin D[58,59]. Another strength to the studies that have identified a significant relationship between vitamin D and disease activity is the method for the determination of serum 25(OH)D, and the consistency throughout the studies. The majority have used RIA methodologies[18,19,21,25,28,30] or chemiluminescent immunoassay[16,22,24,29], with one study not reporting the method[12] and another study using the hospital laboratory[23] which does not state the method used. Although there is no worldwide gold standard for the determination of serum 25(OH)D, the Food Standards Agency has reviewed a number of methods and recommended the liquid chromatography–tandem MS as the preferred method[60]. RIA has been the most common method used in the studies reviewed here. Albeit, a newer less time-consuming approach for vitamin D analysis, not involving the use of radioisotopes is the enzyme immunoassay, which has been used by a number of authors[20,21,26]. With the availability of less cumbersome and automated methods, we may see a greater variety of methods for the quantification of vitamin D in the literature. This in turn may be problematic when comparing results between studies as the enzyme immunoassay has been shown to report significantly higher serum 25(OH)D concentrations when compared to the RIA ($P<0{\cdot}001$)[61] and results from both the enzyme immunoassay and RIA show greater vitamin D concentrations when compared to liquid chromatography–tandem MS[62].

Both the 25(OH)D_2 and 25(OH)D_3 metabolites contribute to total serum 25(OH)D concentrations and therefore, a laboratory method capable of measuring the two may shed further light on vitamin D metabolism in SLE. An additional study used a method capable of measuring the 25(OH)D_3 metabolite only[19]; therefore, total vitamin D status could have been underestimated in this particular study. The consequences of variations between methods can be misclassification of vitamin D deficiency or inadequacy[63], resulting in miscalculation of the prevalence of vitamin D inadequacy within these groups, having a direct impact on statistical analysis comparing disease activity in SLE patients with adequate and inadequate status. This was a study with in excess of 100 SLE patients and recruitment was within a strict time frame of March to May, to rule out any seasonal variation in the vitamin D results. Although vitamin D did not correlate with SLEDAI, there was a positive correlation with levels of complement, which is a clinical component to the disease activity assessment of SLAM but not SLEDAI. Therefore, if another tool using a combination of both laboratory tests and clinical assessment was employed an association between low vitamin D and a greater disease activity may have been apparent.

Effect of diet, supplement use and medication on vitamin D

Critical factors that have not always been evaluated in studies carried out to date examining vitamin D status and disease activity in SLE include ethnicity, photosensitivity, dietary vitamin D intake, sunshine exposure, sunscreen use and interactions between vitamin D and medications prescribed to treat the symptoms of SLE.

Individuals with darker pigmented skin require more UVB light to synthesise vitamin D and not all studies evaluated in this review have detailed the ethnicity of the SLE patients[19,22,24] or have included cohorts with mixed ethnicity and not controlled for this in the analysis[17,18,26]. In addition to UVB synthesis on the skin, vitamin D can be obtained from dietary sources, dietary supplements and fortified foods, with each contributing to vitamin D status. No study has controlled for dietary intakes despite its importance in contributing to status particularly during the autumn/winter. Photosensitivity is another factor not controlled for in the analysis. Sun avoidance is recommended for SLE patients during 11.00 hours and 15.00 hours, from March through to September[64], the hours during which vitamin D can be synthesised on the skin. This in addition to recommendation for photo protection using broad spectrum sun protection[65] further reduces the potential for cutaneous synthesis of vitamin D putting SLE patients, in particular those who are photosensitive, at risk of vitamin D deficiency.

Prophylactic Ca and vitamin D supplements are commonly prescribed alongside steroids in SLE to counteract the negative impact corticosteroids have on bone metabolism. Most of the cited studies have provided information on Ca/vitamin D usage although few report controlling for this in the analysis[18,25]. Some have excluded SLE patients taking Ca and vitamin D supplements[17] or those taking medications that affect bone metabolism[19]; however, others do not provide any information[22–24]. A common course of treatment for SLE patients experiencing flares of disease activity are steroids, which are often prescribed with Ca and vitamin D supplements. Therefore, it is probable that those with the most active disease have higher serum 25(OH)D concentrations due to these supplements, which may mask any relationship.

Insufficient details have been included as to the combination of drugs the patients are prescribed, especially the drugs prescribed to patients taking high dose vitamin D. This could be problematic if those SLE patients with greater disease activity are prescribed an arrangement of medications, some of which have been shown to impact upon vitamin D metabolism[8,9,34,66,67]. Hydroxychloroquine, an anti-malarial drug, has been shown to reduce the synthesis of 1,25-dihydroxyvitamin D_3 in sarcoidosis patients via the inhibition of macrophages[68] and others have reported SLE patients prescribed hydroxychloroquine to have significantly lower 1,25-dihydroxyvitamin D_3 concentrations[29,33]. Furthermore, rosuvastatint, a statin medication, has been shown to increase serum 25(OH)D concentrations of hyperlipidemic patients[67]. Consistency is needed in the design of studies to incorporate all clinical features and factors that affect vitamin D status in an

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attempt to fully understand the impact vitamin D has on disease activity.

Conclusion and future work

Several important issues have been highlighted, specifically related to vitamin D, which subsequently need to be considered in the methodological design of future studies which aim to examine the relationship between vitamin D and disease activity in SLE. It is imperative that the method to score disease activity in SLE is adequately considered, choosing a combination of clinical assessment of charts, laboratory measures and clinical interview to determine the score of disease activity in SLE.

There is a high prevalence of vitamin D inadequacy in SLE. If the studies that have used cut-offs lower than 75 nmol/l serum 25(OH)D to denote adequate vitamin D status, were to use a 75 nmol/l threshold, then a greater proportion of SLE patients evaluated in this review would present with inadequate vitamin D status. Furthermore, evidence is accumulating to suggest that liquid chromatography–tandem MS is the gold standard for measuring serum 25(OH)D and that other methods can overestimate vitamin D status and therefore, there could be a higher incidence of vitamin D deficiency in SLE due to overestimation in methods used to date.

Literature is accumulating in relation to vitamin D and disease activity in SLE, with nine of the fifteen studies evaluated reporting that higher vitamin D concentrations were associated with lower indices of disease activity. No study so far which has examined the relationship between vitamin D and disease activity in SLE has included all the key determinants to vitamin D status. More recent research suggests that there may be a specific effect of vitamin D on fatigue, which is one of the elements assessed in the SLAM and is a particularly debilitating symptom for SLE patients. This review demonstrates the need for a well-designed observational study controlling for ethnicity, diet, medication use, dietary supplements, UV beta exposure and seasonality as well as using a sensitive method for measuring vitamin D status and disease activity in SLE to conclusively establish the role of vitamin D in SLE.

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